REMARKS

In response to the Restriction Requirement, Applicants elect to prosecute the claims of Group II, claims 1-11, drawn to antibodies to the polypeptide of SEQ ID NO:3, methods of preparing and pharmaceutical compositions thereof, with traverse. Applicants traverse on several grounds.

Applicants object to the Examiner dividing the subject matter of Applicants claimed invention, as claimed in Markush format, into multiple restriction Groups. The Examiner's attention is directed to the Patent Office's own requirements for Markush practice, set forth in the 7th edition of the M.P.E.P. (July 1998, February 2000 Revision) at § 803.02 regarding restriction requirements in Markush-type claims:

> **PRACTICE RE MARKUSH-TYPE CLAIMS**
>
> If the members of the Markush group are **sufficiently few in number or so closely related** that a search and examination of the entire claim can be made without serious burden, the examiner must examine all claims on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction.
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> Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas*, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), **it is improper for the Office to refuse to examine that which applicants regard as their invention**, unless the subject matter in a claim lacks unity of invention. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, **unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility**.
>
> This subsection deals with Markush-type generic claims which include a plurality of alternatively usable substances or members. In most cases, a recitation by enumeration is used because there is no appropriate or true generic language. A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s). In applications containing claims of that nature, **the examiner may require a provisional election of a single species** prior to examination on the merits. The

provisional election will be given effect in the event that the Markush-type claim should be found not allowable. Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration.

As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D, and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD, or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the nonelected species would be held withdrawn from further consideration. As in the prevailing practice, a second action on the rejected claims would be made final.

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry. [emphasis added]

As can be seen from the above, it is clear that the present Restriction Requirement does not meet the Patent Office's own requirements.

First, the number of "members of the Markush group are **sufficiently few in number or so closely related** that a search and examination of the entire claim can be made without serious burden, the examiner must examine all claims on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure

described below and will not require restriction." Withdrawal of the restriction requirement as between the **four** specific sequences each in the claims is required on that basis alone.

Second, **it is improper for the Office to refuse to examine that which applicants regard as their invention**, unless the subject matter in a claim lacks unity of invention. ... Broadly, **unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility**." Clearly, the antibodies directed to the four polypeptides of the instant invention share both a common utility and structural feature, based on their classification ability to detect subunits of the same protein, namely NADH dehydrogenase. See page 2, lines 21-25. All of these antibodies could be used to detect intact NADH dehydrogenase.

Third, even if the claims could be considered to be "Markush-type generic claims which include a plurality of alternatively usable substances or members," it is further noted that the M.P.E.P states that "A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other member(s). In applications containing claims of that nature, **the examiner may require a provisional election of a single species** prior to examination on the merits." As the present 12-way restriction is tantamount to a three-way restriction and a requirement for an election of species among the four sequences, this applies in the present case as well.

Therefore, it is respectfully submitted that, upon searching and examining the invention related to antibodies to SEQ ID NO:3 and finding no prior art over which those antibodies can be rejected, the Examiner must extend the search of the Markush-type claim to include the non-elected species, namely the inventions related to antibodies specific for the polypeptides of SEQ ID NO:1, SEQ ID NO:5 and SEQ ID NO:7 as well.

Applicants respectfully submit again that there is minimal additional burden on the Examiner to examine entirety of Applicants claims in addition to the antobodies elected herein, particularly in view of the searches and examination which were already conducted with respect to

the previously issued claims and the additional burden on Applicants to file, prosecute and maintain numerous additional applications in this family, and respectfully request that the Examiner consider doing so.

Morever, Applicants traverse the restriction between the claims of Groups II (1-11), VI (claim 12) and X (claim 13). All three Groups include methods of using antibodies that bind, *inter alia*, a polypeptide of SEQ ID NO:3. A proper search for the claims of Group II, which are directed to antibodies and pharmaceutical compositions containing them, as well as methods of making them, would substantially encompass the methods of using them for detection and purification of the polypeptide of SEQ ID NO:3. Claims directed to methods of making and using the antibodies of Group II can and should be examined together with the respective product claims from which they depend, per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants additionally submit that in any case, there is minimal additional burden on the Examiner to examine those claims in addition to the claims of Group II, particularly in view of the additional burden on Applicants to file, prosecute and maintain yet additional applications in this family, and respectfully request that the Examiner consider doing so.

Finally, Applicants respectfully request that the Examiner also consider examining newly added claim 14 along with the claims previously presented. It is clear that, in order to properly examine the antibody claims, the Examiner is going to be required to first conduct a patentability search based on the polypeptide to which the antibodies bind specifically. Therefore, there is clearly no additional burden on the Examiner to fully search the claimed polypeptides at the same time, and respectfully request that the Examiner consider doing so.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This form is enclosed in duplicate.

Respectfully submitted,

INCYTE GENOMICS, INC.

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Diana Hamlet-Cox
Reg. No. 33,302
Direct Dial Telephone: (650) 845-4639

3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 845-4166

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended, and Claim 14 added as follows:

1. An isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of:

a) an amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7,

b) a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7,

c) a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.

2. A pharmaceutical composition comprising the antibody of claim 1 in conjunction with a suitable pharmaceutical carrier.

3. A method of preparing a polyclonal antibody with the specificity of the antibody of claim 1 comprising:

a) immunizing an animal with the polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, or an antigenically-effective fragment thereof under conditions to elicit an antibody response;

b) isolating animal antibodies; and

c) screening the isolated antibodies with the polypeptide thereby identifying a polyclonal antibody binds specifically to the polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.

4. An antibody produced by a method of claim 3.

5. A pharmaceutical composition comprising the antibody of claim 4 in conjunction with a suitable pharmaceutical carrier.

6. A method of making a monoclonal antibody with the specificity of the antibody of claim 1 comprising:

a) immunizing an animal with the polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, or an antigenically-effective fragment thereof under conditions to elicit an antibody response;

b) isolating antibody producing cells from the animal;

c) fusing the antibody producing cells with immortalized cells in culture to form monoclonal antibody-producing hybridoma cells;
d) culturing the hybridoma cells; and
e) isolating from the culture monoclonal antibodies which binds specifically to the polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.

7. A monoclonal antibody produced by a method of claim 6.

8. A pharmaceutical composition comprising the antibody of claim 7 in conjunction with a suitable pharmaceutical carrier.

9. The antibody of claim 1, wherein the antibody is:
(a) a chimeric antibody;
(b) a single chain antibody;
(c) a Fab fragment; or
(d) a $F(ab')_2$ fragment.

10. The antibody of claim 1, wherein the antibody is produced by screening a Fab expression library.

11. The antibody of claim 1, wherein the antibody is produced by screening a recombinant immunoglobulin library.

12. A method for detecting polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7 in a sample comprising the steps of:
a) combining the antibody of claim 1 with a sample under conditions to allow specific binding; and
b) detecting specific binding, wherein specific binding indicates the presence of polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7 in the sample.

13. A method of using an antibody to purify polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7 from a sample, the method comprising:
a) combining the antibody of claim 1 with a sample under conditions to allow specific binding; and
b) separating the antibody from the protein, thereby obtaining purified polypeptide of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.

14. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:
a) a polypeptide having an amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.

b) a naturally-occurring polypeptide having an amino acid sequence at least 90% identical to the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7,

c) a biologically-active fragment of the polypeptide having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7, and

d) an immunogenic fragment of the polypeptide having the amino acid sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:7.